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Adult-onset autosomal dominant myoclonic epilepsy: Report of a family with an overlooked epileptic syndrome

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Summary

Objective: Myoclonic epilepsy is a common epileptic syndrome with high genetic contribution. We described a pedigree in which 10 individuals presented with a non-progressive, adult-onset myoclonic epilepsy.
Materials and methods: The pedigree was constructed and analyzed. Six affected members were studied with clinical grounds, mental status, neurophysiology, video-electroencephalographic (EEG), brain magnetic resonance imaging (MRI) and mutational analysis of *GABRA1* (*GABRA1A*, which endoces the α1 subunit of the γ-aminobutyric acid receptor subtype A). Clinical and EEG data were collected from six unaffected members.
Results: Autosomal dominant hereditary was shown. The age of seizure onset was approximately 40. All the individuals had myoclonic seizures and a normal cognitive level. Bilateral symmetric jerks of the shoulders, arms or legs featured the myoclonic seizure. Ictally, the consciousness was not affected. The ictal EEG demonstrated bilateral spikes-and-waves. The occurrence of myoclonic seizures was not associated with sleepiness. Rare generalized tonic-clonic seizures occurred in two individuals. No absence or accompanying involuntary movements were observed. A lower dose of valproic acid (200—500 mg/D) (clonazepam 0.5 mg/D in a patient) was required to stop the myoclonic seizures.
Conclusions: The clinical features of late adult-onset autosomal dominant myoclonic epilepsy are similar to juvenile myoclonic epilepsy (JME), which is a common generalized epileptic syndrome with a significant hereditary component. But the age of

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onset, rare association of other seizure patterns, and non-relation of seizure onset to sleepiness suggest that this may be a distinct familial epileptic syndrome different from recognized familial myoclonic epilepsies.

Introduction

Many epileptic syndromes, currently recognized by the International League Against Epilepsy (ILAE), fit the original operational definition of idiopathic generalized epilepsy (IGE) syndrome.[1,2] These IGE syndromes, which can affect children, adolescents, and young adults, exhibit some overlap: absence, myoclonic seizures, and tonic-clonic seizures, and the electroencephalographic (EEG) hallmark of paroxysms of generalized spike-wave. Recent studies reported that onset after the age of 20 years is not rare.[3,4] Familiarity often shows in those patients with adult-onset generalized seizure with myoclonus, myoclonic epilepsy, or both. A mutation of the α-1 subunit of the γ-aminobutyric acid receptor (*GABRA1*) has been firstly found in a French-Canadian family with autosomal dominant heredity of a phenotype consistent with juvenile myoclonic epilepsy (JME), a common IGE syndrome.[5]

In 2002, we found four members of an East-Taiwanese aboriginal family with epilepsy. Until 2006, 10 affected family members have had a similar phenotype. The affected members experienced myoclonic jerks that began in their 30s and 40s. We studied the clinical features, brain structure, intelligence, electroencephalographic activity and neurophysiology of the members with or without myoclonic jerks. We also analyzed the sequence of *GABRA1*, and attempted to identify specific clinical and EEG features of the epileptic syndrome. In this study, we aimed to classify and report the familial myoclonic epilepsy, a syndrome or a seizure subtype that may be not recognized.

Materials and methods

The proband (II-5) of a family from Hualien, East Taiwan, a 50-year-old man, was referred to our epilepsy center for seizure treatment. This male patient had a substantial family history positive for myoclonic jerks. A detailed family pedigree was constructed by collecting clinical histories on all affected and unaffected individuals and their spouses. There were 10 affected members (of whom 9 are alive) over four generations. We obtained genealogical information on 63 family members (including 16 spouses), and conducted an evaluation of 12 individuals (Fig. 1). All study participants were provided informed consent.

Blood samples were collected from 11 members (including patients II-1, II-3, II-4, II-5, III-3, and III-10) after informed written consent. Genomic DNA was extracted using standard techniques from peripheral blood leukocytes. Sequence analysis of *GABRA1* was amplified from genomic DNA using intronic primers 5′TGCCATTCCATGAATCACAG3′ and 5′TCATGGCACTTAATTGTTTACG3′. The sequence of each amplicon was confirmed by sequencing in both directions. Sequences were compared with the reference *GABRA1* mRNA sequence (GenBank NM_000806).

Long-term video-EEG monitoring with a standard International 10-20 system setting was performed on six affected individuals (patients II-1, II-3, II-4, II-5, III-3, and III-10). An EEG recording that included sleep was also performed on five clinically unaffected individuals. The recording included hyperventilation and photic stimulation. Somatosensory evoked potentials (SEPs) were recorded from centroparietal (C3′, C4′ = 2 cm behind the International

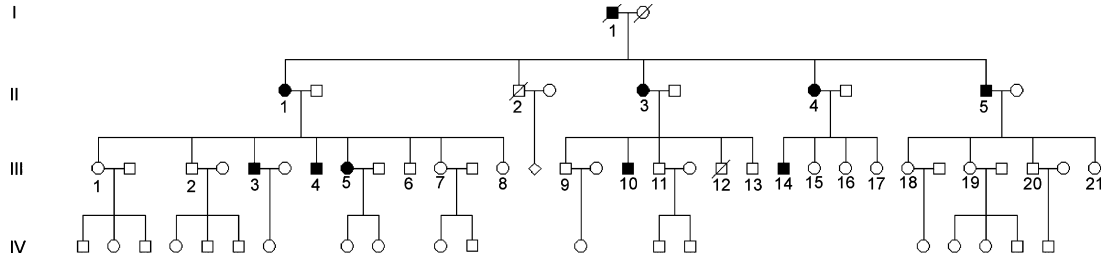

Figure 1 The pedigree of East-Taiwanese aboriginal kindred affected with myoclonic epilepsy suggests an autosomal dominant inheritance pattern. The age of the oldest fourth generation member is 27 years.

10-20 system C3 and C4) regions, at the seventh cervical level, and from Erb's point, using referential montages. Median nerve stimulation (0.2 ms pulse width with four pulses per second in 500 trials) was performed on four affected individuals (patients II-1, II-3, III-3, and III-10).

We examined the intellectual abilities on five affected individuals (patients II-1, II-3, II-4, II-5, and III-10) with the administration of the Wechsler Adult Intelligence Scale-III (Chinese version). Each affected family member underwent brain magnetic resonance imaging (MRI) with 1.5 T instrumentation (axial T2-fluid-attenuated inversion recovery (FLAIR), axial spoiled gradient recalled echo (SPGR), axial diffusion tensor MRI (DTI), and sagital T1).

Results

Ten members of the affected family (six men and four women, including the first generation) experienced myoclonic seizures. An autosomal dominant inheritance pattern with high penetration was observed (Fig. 1). The age of onset of the affected individuals ranged from 35 to 42 years. The age of the oldest fourth generation member was 27 years. No similar symptom or presentation of febrile convulsion was observed in the fourth generation members. In second and third generation family members, no febrile seizure or a history of convulsion were reported prior to myoclonic seizure development.

In the affected family members, the myoclonic jerks usually occurred as a single episode throughout the day. On average, the frequency of mylconic seizures was once daily, and the seizure might be associated with a fall. There usually was no obvious alternation of consciousness. The affected family members could not ascertain whether or not the myoclonic jerks occurred during sleep. Alcohol or menstruation did not affect the number of seizures. Fatigue tended to increase the number of myoclonic jerks experienced by the patients. However, the jerks did not group into a cluster. Typically, the myoclonic seizures were characterized by bilateral symmetric involvement of the shoulders and limbs, and were not associated with noticeable changes in consciousness. If the myoclonic jerk affected the lower extremities, hyperextension of the legs led to an unpredicted slump. (This was the experience of patients II-1, II-3, and II-5.) On neurological examination, no neurological deficit was identified and no movement disorders, such as choreoathetosis or astasis, were observed.

Five myoclonic seizures (three seizures in patient II-1 during light sleep, early morning, and daytime, respectively; one seizure in patient II-3 in the early morning; and one seizure in patient III-3 during the daytime) were recorded. The seizure onset was in

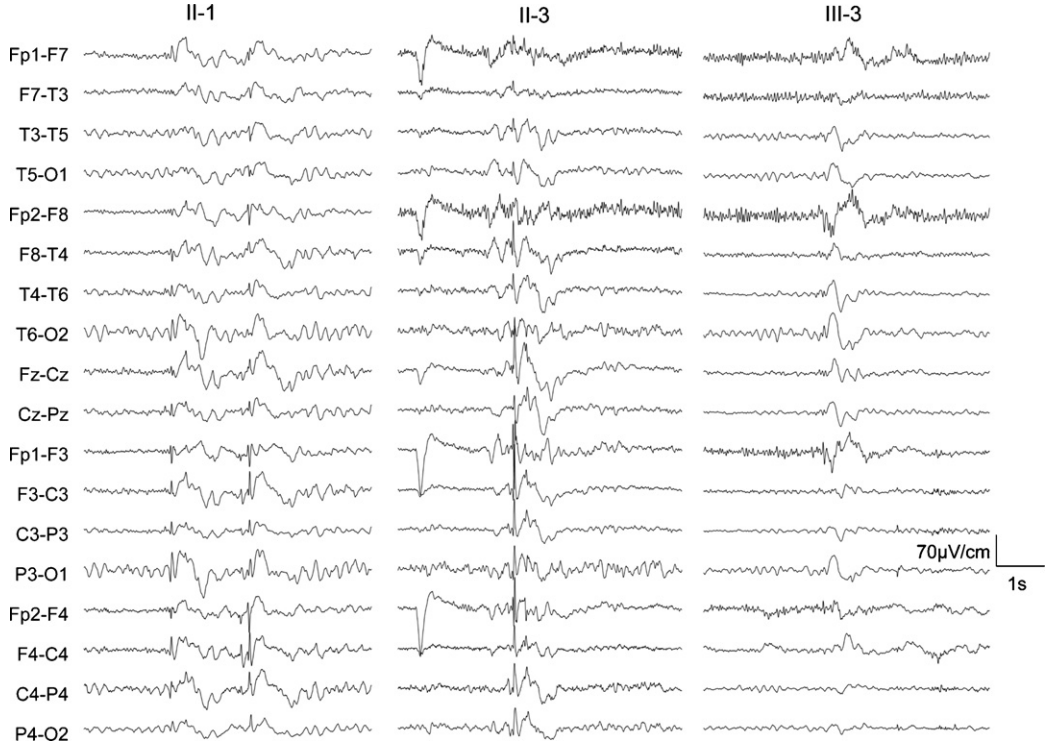

Figure 2 The ictal EEGs from patients II-1, II-3, and III-3 show bilateral spike-and-waves.

accordance with spike/polyspike-and-waves or spike-and-wave complexes (Fig. 2). In the long-term EEG recordings, bilateral synchronous spike/polyspike-and-waves appeared in all behavior states including the slow-wave- and REM-sleep stages (in patients II-1, II-3, and II-5). The epileptiform activity was not shown in the standard EEG registrations of non-affected members. Photic stimulation did not provoke EEG responses in the six patients and six non-affected members.

Sequence alignments and comparisons with the wild-type sequence (GenBank NM_000806) did not indicate any deletion or point mutation. The *GABRA1* Ala322Asp mutation was not observed in any sampled member. Full scale IQ ranged from 90 to 104 in the five patients submitted to the entire scale. No figure for the performance IQ was greater or lesser than the verbal IQ was shown. The SEP studies did not show increased amplitude or prolonged latency of scalp potential amplitude. The brain MRI scans did not depict any structural disorder.

A low dose of valproic acid (range, 200—500 mg per day) was required to stop the myoclonic seizures. The myoclonic seizures relapsed within 2 days after drug discontinuation. This occurred despite the fact that patients II-1 and II-3 were seizure free for a 2-year period. Intrafamilial variation was limited. Two probands (patients II-3 and II-4) experienced rare generalized tonic-clonic convulsions (GTC). The GTCs did not recur since the valproic acid was administrated (Table 1).

Discussion

In this presentation of non-progressive, adult-onset, autosomal dominant myoclonic epilepsy in a four-generation family in East Taiwan, we could not provide a recognized syndromic diagnosis for some of the clinical features.

Primary IGE is commonly thought to arise in childhood or adolescence, but Gastaut reported a high prevalence of adult-onset IGE (in up to 35% of patients) in 1981.[3] In 2003, Marini et al. identified 121 patients with IGE in whom 34 had seizures that started at the age of 20 years or thereafter, with 5 of the 34 patients commencing seizures after the age of 40. Adult-onset IGE also had common clinical features: generalized spike/polyspike-and-wave EEG activities, good antiepileptic drug response, favorable prognosis, probable genetic basis, and normal brain.[4] These cardinal features are not prominently different from JME or our affected family members.

Juvenile myoclonic epilepsy is a common form of IGE representing 5—10% of all epilepsy cases.[6] Approximately, 17—50% of patients have a family history of epilepsy.[7] Individuals most commonly present between the ages of 8 and 26 with myoclonus. The myoclonus is characterized by early morning attack and symmetric jerks of the upper limbs, as well as precipitated by fatigue, alcohol, and menstruation. Over 90% also have generalized tonic-clonic seizures, and 30% experience absence seizures. The response to anti-convulsant monotherapy such as

Table 1 Clinical and EEG data of adult-onset autosomal dominant myoclonic epilepsy kindred

Patients		IQ			Epilepsy			
Pedigree reference	Age (years)	FSIQ[a]	VIQ[b]	PIQ[c]	Age at onset (years)	Type of seizures	Epileptiform EEG discharges	Dosage of valproic acid (mg/day)
II-1	68	96	95	99	38	Myoclonic	SW[d]	200
II-3	59	90	89	95	35	Myoclonic	SW, PSW[e]	200
II-4	56	99	98	101	42	Myoclonic	SW	200
II-5	51	101	102	99	40	Myoclonic, GTC[f]	SW, PSW	200
III-3	45	NA[g]	NA	NA	38	Myoclonic, GTC	SW, PSW	500
III-4	41	NA	NA	NA	37	Myoclonic	SW	200
III-5	39	NA	NA	NA	38	Myoclonic	SW, PSW	0.5[h]
III-10	37	104	102	98	36	Myoclonic	SW	200
III-14	36	NA	NA	NA	35	Myoclonic	SW	200

The routine scalp EEG from proband III-1, III-2, III-9, III-11, IV-1, and IV-2 did not detect any abnormal EEG activity.
[a] FSIQ: full-scale IQ.
[b] VIQ: verbal IQ.
[c] PIQ: performance IQ.
[d] SW: spike-and-waves.
[e] PSW: polyspike-and-waves.
[f] GTC: generalized tonic-clonic seizure.
[g] NA: not available.
[h] Proband III-5 has clonazepam 0.5 mg per night.

sodium valproate is good. Relapses occur frequently after the discontinuation of medication.[8] In our affected individuals, the age of seizure onset was greater than in JME patients. The affected probands did not experience photosensitivity. Episodes of myoclonic jerks would occur in almost all behavioral states. These clinical features were distinguishable from JME.

It is well established that hereditary contributes the etiology of JME. Cossette et al. reported an interesting finding in the area of JME genetics.[5] An Ala322Asp mutation in the *GABRA1* gene that codes for the α1 subunit of the γ-aminobutyric acid receptor subtype A ($GABA_A$) was found in the affected members of a large French-Canadian family exhibiting the autosomal dominant form of JME. This mutation in *GABRA1* is the first known mutation that segregates with the classical JME clinical phenotype. All affected individuals in this family were heterozygous for a C $\rightarrow$ A substitution in exon 9 of *GABRA1*, which is predicted to change a GCC (alanine) to a GAC (aspartic acid) codon at position 322 of its cDNA. Each affected family member presented similar clinical features, with myoclonus and GTCs. Some of them also presented absence seizures. The EEG abnormalities found in affected members of the family showed generalized polyspike-and-wave epileptic discharges, which would occur spontaneously or be precipitated by photic stimulation. The mean age of onset was 11.8 years. Our affected family members had myoclonic seizures at a mean age of 37.5 years. Although *GABRA1* Ala322Asp mutation contributed to the generation of myoclonic seizures, we did not observe this in our affected individuals. Shaochun et al. and Kapoor et al. systemically screened the Ala322Asp mutation in JME families with exhibiting dominant inheritance from Europe and India, respectively.[9,10] This mutation did not appear.

Two recently reported myoclonic epileptic syndromes, benign familial autosominal dominant myoclonic epilepsy and autosomal dominant cortical reflex myoclonus and epilepsy, share similar characteristics, including autosomal dominant heritance, adult-onset, non-progressive course, cortical myoclonus, generalized seizures, and giant SEP.[11–13] However, our patients did not have cortical tremors, a photoparoxysmal response, or giant scalp SEPs.

Actually, the clinical and EEG features of our affected members resembled patients in the study by Marini et al., who are described as ''adult onset myoclonic epilepsy''.[4] Marini and colleagues categorized six patients into the ''subsyndrome''. These patients presented with myoclonic jerks and GTCs at a mean onset age of 37. The seizures and EEG of another case of a 75-year-old woman in the same study were strikingly similar. She had dominant jerks of the upper limbs, and generalized polyspike-wave of EEG activity. Only two probands of our patients had a history of GTCs. They were not supposed to have absences. However, no member of the fourth generation had myoclonic seizure. We assume that the onset age does not achieve. We expect to find new affected members in the fourth generation in the coming decade.

Conclusion

Work on the classification of epileptic syndromes is ongoing. Many syndromes are still under discussion. The non-progressive, adult-onset, autosomal dominant myoclonic epilepsy described here appears to have remarkable features that clearly distinguish the condition from other recognized myoclonic epilepsies. The epileptic syndrome may be a variant of JME or a variety of subsyndrome. Genetic analysis should help to clarify the etiology and pathophysiology of this myoclonic epilepsy.

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